Evaluating the Effect of Inequalities in Oral Anti-coagulant Prescribing on Outcomes in People with Atrial Fibrillation

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Abstract

Background

Whilst anti-coagulation is typically recommended for thromboprophylaxis in atrial fibrillation (AF), it is often never prescribed, or prematurely discontinued. The aim of this study was to evaluate the effect of inequalities in anti-coagulant prescribing by assessing stroke/systemic embolism (SSE) and bleeding risk in people with AF who continue anticoagulation compared with those who stop transiently, permanently, or never start.

Methods

This retrospective cohort study utilised linked Scottish healthcare data to identify adults diagnosed with AF between January 2010 and April 2016, with a CHA2DS2-VASC score of ≥2. They were sub-categorised based on anti-coagulant exposure: never started, continuous, discontinuous, and cessation. Inverse probability of treatment weighting-adjusted Cox regression and competing-risks regression were utilised to compare SSE and bleeding risks between cohorts during five year follow-up.

Results

Of an overall cohort of 47,427 people, 26,277 (55.41%) were never anti-coagulated, 7,934 (16.72%) received continuous anti-coagulation, 9,107 (19.2%) temporarily discontinued and 4,109 (8.66%) permanently discontinued. Lower socio-economic status, elevated frailty score, and age ≥75 were associated with a reduced likelihood of initiation and continuation of anti-coagulation. SSE risk was significantly greater in those with discontinuous anti-coagulation, compared to continuous (SHR: 2.65; 2.39-2.94). In the context of a major bleeding event, there was no significant difference in bleeding risk between the cessation and continuous cohorts (SHR 0.94; 0.42-2.14).

Conclusion

Our data suggest significant inequalities in anti-coagulation prescribing, with substantial opportunity to improve initiation and continuation. Decision-making should be patient-centered and must recognise that discontinuation or cessation is associated with considerable thromboembolic risk not offset by mitigated bleeding risk.

Lay Summary

Our study used routinely collected health data in Scotland to assess the effects of stopping anti-coagulation medications in people with atrial fibrillation. Key findings:

- There is considerable inequality in the prescribing of blood-thinning medications
• Stopping blood-thinning medication is associated with a greater risk of stroke and does not reduce risk of bleeding

Keywords: atrial fibrillation, stroke, pharmacoepidemiology, real-world data

Introduction

Background/Rationale

Despite the high thromboembolic risk in the AF population, stroke prophylaxis with anticoagulants is frequently under-utilised or prematurely discontinued, generally due to the monitoring requirements of warfarin or a perceived high risk of bleeding. (1) Indeed, the likelihood of older adults and females being anti-coagulated is paradoxically lower, despite their higher stroke risk. (2) A prior observational study of people with non-valvular AF (NVAF) prescribed warfarin in a national dataset combining Medicare and insurance claims data, reported that the risk of ischaemic stroke is approximately doubled in those that discontinued warfarin compared to those with continuous prescriptions. (3) A study of 1361 individuals with NVAF prescribed an alternative vitamin K antagonist, acenocoumarol, at an anti-coagulation centre in Spain suggested that cessation of anti-coagulation is associated with increased stroke, adverse cardiovascular events and all-cause mortality. (4) Whilst the acute treatment of those with bleeding associated with anti-coagulation often requires immediate discontinuation of anti-coagulation, the ongoing management is complex; clinical decision-making must consider the competing risks of a thromboembolic event if anti-coagulation is withheld, and a recurrent bleed if it is recommenced, and clinical consensus is currently lacking as to the optimal approach. (5) Whilst there is an increasing body of literature around patterns of adherence to anti-coagulation, few studies have evaluated the clinical outcomes associated with discontinuation of anti-coagulation in individuals with AF, particularly in the context of a major bleeding event.

All individuals in Scotland are assigned a unique identification number, the Community Health index (CHI) number, creating a record of engagements with health and social care facilities through the lifetime. (6, 7) Linkage of national databases by CHI number affords the opportunity to analyse rich Scotland-wide individual patient data; this real-world data may be leveraged to explore research questions, such as the impact on clinical outcomes of discontinuing oral anti-coagulation in people with AF for which a randomised-controlled trial may be infeasible. (8-11)

Objectives

The primary objective of this study was to evaluate the effect of inequalities in anti-coagulant prescribing by comparing the risks of stroke/systemic embolism (SSE) in adults with AF with
discontinuous exposure to anti-coagulation, versus those never started on anti-coagulation, and those with continuous anti-coagulation, respectively. The secondary objective was to assess the effect of inequalities in anti-coagulant prescribing by comparing the risk of SSE and bleeding in those that received continuous OAC therapy with those that discontinued anti-coagulation in the context of a major bleeding event.

Methods

Study Design

This was a retrospective observational cohort study of adults hospitalised with an incident AF event in Scotland.

Data Sources and Cohort

Methods are reported in accordance with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines (Supplementary Materials).(12) Public Health Scotland (PHS) provided access to fully anonymised data in support of a broader study which utilised routinely collected healthcare data to assess the comparative effectiveness of anticoagulation for stroke prevention in people diagnosed with AF.

All adults aged 18 or older with a first diagnosis of AF between 1st January 2010 and April 30th 2016 with a CHA₂DS₂-VASC score (inclusive of one point for female sex) of two or greater were identified from Scottish Morbidity Records (SMR) 01, which records inpatient and day case discharges for all specialities excluding psychiatry and obstetrics. The AF cohort in SMR01 was delineated by ICD-10 coding in any diagnostic position(I48). We triangulated this with data from the Scottish Stroke Care Audit (SSCA), which collected information from all Scottish hospitals managing strokes, including whether AF had been diagnosed. There was considerable overlap when merging the datasets, with 16.9% of the records from SSCA unmatched with SMR01.

Patient-level data linkage was undertaken with National Records of Scotland (NRS) (mortality data) and Prescribing Information System(PIS) (prescribing data)(Figure 1). The National Records of Scotland dataset is the gold-standard mortality dataset in Scotland; whilst it is not validated, data-entry is double-coded and previous audits indicate high data quality.(13) Data linkage was also completed with SMR00 (outpatient appointments) to ensure relevant comorbidities were captured to inform calculation of CHA₂DS₂-VASC and HAS-BLED scores.
Stroke and bleeding events were measured using International Classification of Diseases (ICD)-10 and Office of Population Censuses and Surveys (OPCS)-4 codes (Supplementary Materials: Table S2) in SMR01. SMR01 includes a Continuous Inpatient Stay (CIS) marker used to link episodes of care from distinct specialties or units within an unbroken period of admission to secondary care, which was used to identify earliest date for clinical event and to avoid multiple counting of the same events. Inpatient data were available from 1st January 2005; the start date of the study was selected based on data availability allowing for a five-year lookback period to identify those whose primary AF diagnosis preceded 1st January 2010. Those identified as having been diagnosed during the look-back period were excluded to avoid double-counting of the incident event. Data was available until 31st May 2021, and individuals were followed-up until the event of interest and were censored at the end of the follow-up period, five years after the index date of AF diagnosis; follow-up was restricted to five years for all patients given that the likelihood of discontinuity in anti-coagulation would be greater in those with longer available follow-up compared to those that only had a minimum of five years of follow-up data available.

Our AF population was divided into four cohorts according to exposure to oral anti-coagulation: ‘never started’, ‘continuous OAC therapy’, ‘discontinuous OAC therapy,’ and ‘cessation of OAC therapy,’ (Table 1). Anti-coagulation is here defined as having been prescribed either warfarin or a DOAC (apixaban, rivaroxaban, dabigatran or edoxaban) for the first time following an AF event. Whilst DOAC prescriptions with dosages less than a minimum therapeutic threshold for prevention of thromboembolic events defined by the British National Formulary (BNF) were excluded, in the absence of availability of international normalised ratio (INR) data, it was assumed that doses of warfarin prescribed were sufficient for thromboprophylaxis. A lookback period of thirty days to the respective index AF diagnosis was implemented to ensure only individuals who were treatment naïve prior to commencing anti-coagulation were included in the analysis. Discontinuation of anti-coagulation was established according to the refill-gap method; those with a temporal gap between consecutive prescriptions of greater than sixty days, not filled by the penultimate prescription, were defined as having discontinued. Prescriptions of oral anti-coagulants were determined from the PIS; this dataset comprises records for the prescribing, dispensing and reimbursement for all prescriptions dispensed by community pharmacies in Scotland. Prescriptions in Scotland are free of charge, with reimbursement data generated from pharmacies based on electronic or paper prescriptions after dispensing. Long-term repeat prescriptions, such as anti-coagulation, are typically prescribed at intervals of 28 or 56 days. To ensure that the indication for the anti-coagulant prescription was exclusively AF, Individuals with valvular heart disease, a mechanical cardiac valve, or venous thromboembolism, were excluded from analyses (Table S3).
Sub-group analyses evaluating risk of SSE, bleeding and mortality, were undertaken for people commenced on anti-coagulation that experienced a major bleeding event.

Data cleaning and pre-processing was undertaken according to established methodologies for routine healthcare data. Since less than 5% of records had missing data, and these appeared to be missing completely at random, imputation of the missing values was not completed; instead, a complete case analysis was undertaken, with those records excluded. Variables with missing data are detailed in Appendix 3 (Table S4).

The propensity score-based Inverse Probability of Treatment Weighting (IPTW) method was utilised to address potential confounding by indication, arising due to lack of randomisation. IPTW was utilised rather than propensity score matching to avoid the exclusion of eligible subjects. Propensity score (PS) estimation was undertaken for the respective AF subgroups to estimate the probability of anti-coagulant exposure status conditional upon the observed baseline characteristics of the AF population. Up to five PS models (never started versus discontinuous OAC therapy, never started versus cessation of OAC therapy, discontinuous OAC therapy versus cessation of OAC therapy, continuous OAC therapy versus discontinuous OAC therapy, continuous OAC therapy versus cessation of OAC therapy) were thus generated for each outcome of interest. Logit models were used to estimate propensity scores and incorporated baseline characteristics which were either of prognostic relevance to the clinical outcomes, or potentially predictive of anti-coagulation status. The models accounted for age (years), sex, and geographical location using an 8-fold urban rurality classification, which was divided into three strata: urban (1-2), small and large towns (3-6), and rural (7-8). An indicator of socio-economic status, the Scottish Index of Multiple Deprivation (SIMD) was also included; this is a ranked scale of multiple deprivation for geographical locations, and was divided into quintiles, such that one represents the most deprived, and five denotes the least deprived areas, respectively. PS also accounted for CHA₂DS₂-VASc at the time of the index AF event. Furthermore, PS for the ischaemic stroke/systemic embolism outcomes also accounted for the following confounding variables: prior stroke/TIA, comorbidity (measured using the Charlson Co-morbidity Index), and an electronic frailty score.

PS for the outcomes for major bleeding also accounted for anti-platelet prescriptions in the two years preceding the index AF event and time (days).

To implement the IPTW methodology, a weight indicative of the probability of either no exposure to anti-coagulation or continuous OAC therapy, and identical to the reciprocal of the aforementioned PS, was applied to individuals in those respective cohorts. Similarly, a weight equivalent to the reciprocal of one minus the PS was allocated to the discontinuous OAC therapy cohort. The risks of two significant clinical events associated with AF, stroke (both
ischaemic and haemorrhagic), major bleeding between discontinuation of anti-coagulation in
individuals diagnosed with AF, was compared for those never prescribed anti-coagulation, and
for those with continuous exposure, using Cox proportional hazards regression (Figure 2).
Doubly robust estimation was implemented by inclusion of the aforementioned propensity
scores within the respective Cox proportional hazards regression models. To mitigate bias due
to residual differences in the baseline covariates, and redress possible covariate imbalance, the
variables included to estimate propensity scores were incorporated into the adjusted models.
Competing risk regression, using Fine & Gray proportional sub-hazards models, was
implemented to establish the first clinical event (SSE or death, and major bleed or death).
Outcomes were evaluated using an intention-to-treat analysis.

Statistical analyses were completed using STATA version 16. Descriptive statistics for
categorical variables are presented as the frequency and percentage in which they occurred,
and as mean and standard deviation for continuous variables. Regression analyses are
presented as hazard ratios with 95% confidence intervals.

Ethics
Ethical approval is not required for the analysis of secondary Scottish administrative healthcare
data. However, the proposal for this study was reviewed and approved by the University of
Glasgow Medicine, Veterinary Medicine and Life Sciences (MVLS) College Research Ethics
Committee. This study was conducted in accordance with International Society for
Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and
applicable regulatory requirements.

Data Availability
The data is confidential, and analyses were subject to disclosure control by PHS. Access to the
data may be requested by application to PHS via the Public Benefit and Privacy Panel.

Results
Characteristics of the AF Cohort
Of an overall cohort of 47,427 people with an incident diagnosis of AF between 1st January 2010
and 30th April 2016 and a CHA2DS2-VASC score of ≥2, those never prescribed anti-coagulations
tended to be older, comprising a considerably greater proportion of people aged older than 85
(Table 2). Sex, urban rurality score, CHA2DS2-VASc scores, and HAS-BLED scores were
comparable between the cohorts. The cohort that never initiated anti-coagulant therapy had
the greatest proportion of individuals in the most deprived SIMD quintile, whilst the continuous
OAC therapy population had the greatest proportion of people categorised within the most affluent quintile. Furthermore, those aged ≥75, or with an elevated frailty score, were less likely to initiate anti-coagulation, and if prescribed, were more likely to discontinue.

The rate of discontinuation appears to be greatest at the extremes of the CHA₂DS₂-VASC score, with rates of 63.4% and 63.5% for scores of 2 and 3, and 63.6% and 67.7% for scores of 7 and 8 respectively. Initiation and continuity of anti-coagulation improved according to year of AF diagnosis (Figure S1). DOACs replaced warfarin as the predominant OAC prescribed over the duration of the study (Figure S2) although OAC discontinuity was comparable between OAC types (Figure S3).

SSE Risk

The percentage diagnosed with stroke or systemic embolism during the five-years after AF diagnosis was highest in the discontinuous OAC therapy cohort (16.54%) and lowest in those that received continuous anti-coagulation (5.99%).

People receiving discontinuous OAC therapy had an increased risk of stroke during the five year follow-up period from an initial AF diagnosis, compared to those that never started oral anti-coagulation (SHR 3.03; 2.81-3.26)(Figure 2A) and those with continuous anti-coagulant prescriptions (SHR 2.65; 2.39-2.94)(Figure 2B). Cessation was associated with greater stroke risk than individuals that never started anti-coagulation (SHR 1.22; 1.22-1.38) (Figure 2B), but lower stroke risk than people in the discontinuous OAC therapy cohort (SHR 0.39; 0.34-0.44)(Figure 4C). There was no significant difference in stroke risk between people that permanently discontinued anti-coagulation and those with continuous OAC therapy. Prior stroke, age greater than 75, co-morbidities, and elevated frailty risk score were significantly associated with a higher risk of stroke. Compared with a reference score of 2, all CHA₂DS₂-VASC scores were associated with a greater risk of SSE. Compared to the most deprived SIMD quintile, the second and third quintiles had similar stroke risk, whilst the fourth and fifth quintiles were associated with a reduced risk of stroke, which was statistically significant. Mortality risk in this population is reported in Supplementary Materials 8.

Discontinuation of OAC therapy was associated with an increased risk of stroke in people that had a prior bleeding event compared to those with continuous OAC therapy (SHR 2.04; 52-2.74)(Figure 3A). Sex, age older than 75, SIMD quintile, urban-rurality classification, time off anti-coagulation and frailty score were not significant mediators of stroke risk in this cohort. Cessation was not associated with a statistically significant difference in risk of stroke compared to those with discontinuous or continuous OAC therapy(Figure 3A/B).
**Major Bleed Analyses**

**Anti-coagulation Prescriptions**

Warfarin was the most common anti-coagulant in our cohort, prescribed to 71.6% of people. Apixaban was the mostly commonly prescribed DOAC (15%), followed by rivaroxaban (11.5%); dabigatran (1.3%) and edoxaban (0.53%) were utilised more rarely.

**SSE Risk**

During five years of follow-up from index AF diagnosis, the highest percentage of stroke and systemic embolism events in individuals with a prior major bleed event, occurred in the discontinuous OAC therapy (33.63%) and cessation (33.33%) cohorts; the continuous OAC therapy population had lowest proportion of stroke events (14.76%).

**Bleeding Risk**

Recurrent bleeding was most frequent in individuals that discontinued anti-coagulation, either temporarily (27.68%) or permanently (20.5%) or were never prescribed it (22.98%).

The discontinuous OAC therapy cohort had a greater risk of a bleeding event compared to those that persisted with anti-coagulation (SHR 1.71; 95% CI: 1.25-2.33)(Figure 4A). The highest category of frailty risk was associated with an increased risk of recurrent bleeding. Mortality risk in this population is reported in Supplementary Materials 9.

**Discussion**

This retrospective cohort study utilised national linked individual patient data to compare the risks of SSE and bleeding in AF according to anti-coagulant exposure, from which there are multiple key observations. Firstly, despite the high thromboembolic risk in our population, the rate of anti-coagulation was low, and the rate of discontinuation was high, although this improved over the duration of our study. There were considerable inequalities in OAC prescribing; lower socio-economic, elevated frailty score and age ≥75 were associated with anti-coagulation not being commenced and non-continuous OAC prescribing. Furthermore, the SSE risk associated with discontinuation of anti-coagulation appears to be at least equivalent to, if not greater, than never commencing anti-coagulation. Finally, our analyses also indicate that discontinuation or cessation of OACs is not protective with regards to the risk of recurrent bleeding.
OAC Prescribing

Although our population had an elevated SSE risk, a considerable proportion, 55.4% never commenced warfarin or a DOAC, which is consistent with prior studies highlighting suboptimal anti-coagulation amongst the AF population. Indeed, a recent study by Lee et al. reported that 49.7% of those diagnosed with AF admitted to hospital in Scotland between 2010 and 2019 were not anti-coagulated, although this had improved from 63.8% in 2010 to 35.5% in 2019. (22) They found that women were less likely to be anti-coagulated, although this disparity was mitigated by the increasing prevalence of anti-coagulation with DOACs. Although our data did not include information on the rationale for decision-making on anti-coagulation, De Breucker et al. previously reported that the absence of anti-coagulation in older adults is likely due to functional or cognitive impairment, falls risk, malnutrition, or depression. (23)

Whilst sustained endeavours to ensure that anti-coagulation is appropriately initiated at diagnosis are clearly integral, it is also concerning that despite AF being a lifelong condition, requiring ongoing thromboprophylaxis, only 37.51% of our population received continuous OAC therapy. We observed a discontinuation rate of 62.49% with comparable discontinuation between DOACs and warfarin, which is consistent with prior studies. Indeed, a retrospective study by Baker et al. of discontinuation (defined as a temporal gap in prescriptions of greater than thirty days) in 41864 individuals with AF in the USA prescribed DOACs, reported discontinuation rates of 60.3%, 52.8% and 62.9% for rivaroxaban, apixaban and dabigatran respectively. (24) Furthermore, in a retrospective cohort study in the US of 12129 adults with AF, 47% discontinued oral anti-coagulation, which occurred within an average of 120 days; first discontinuation often occurs early after the initial prescription. (25)

Some studies considered adherence and persistence, rather than, or in addition to, discontinuation explicitly, in their analyses. Indeed, Dhamane et al. conducted a retrospective analysis of non-persistence, defined as treatment switching, or a refill-gap of 60 days or greater, in over one million people with AF prescribed anti-coagulants in the US. (26) At one year, the cumulative incidence of non-persistence was 51.3%, 58.9%, 51.3% and 52.2%, for warfarin, apixaban, rivaroxaban and dabigatran, respectively. Few studies have evaluated cessation of anti-coagulation; a prospective cohort study in Italy assessing cessation of DOACs in 1305 adults with AF reported that 15.4% were no longer anti-coagulated after one year of follow-up; greater than 60% discontinued within the initial 6 months. (27)

Our analyses also suggest considerable inequalities in OAC prescribing, which are essential to address, given that non-initiation and discontinuity of anti-coagulation are associated with poorer clinical outcomes, including a greater SSE risk. For example, those living in the most...
deprived areas were most likely to have never commenced anti-coagulation, whilst those living in the most affluent areas were most likely to have been prescribed anti-coagulation. A previous study of stroke survivors with AF in Scotland found that the most deprived SIMD quintiles were associated with an absence of anti-coagulation. (28) Furthermore, those in the least deprived quintile were most likely to have continuous anti-coagulation, which is consistent with international studies (29, 30). However, in a recent study of trends in OAC prescribing in England, a higher socio-economic status appeared to be associated with non-adherence. (31)

**Stroke Risk Following OAC Discontinuation**

Our analyses indicate that OAC discontinuation is associated with a significantly increased SSE risk in adults with AF, compared to those that are continuously anti-coagulated. Indeed, Toorop et al. evaluated OAC persistence in a Dutch AF cohort, defined as a gap of less than one hundred days between the final OAC prescription and the study end date, and found that non-persistence was associated with a 58% increase in the risk of ischaemic stroke compared to those with continuous OAC exposure. (32) Similarly, Rodriguez et al. conducted a nested case-control analysis of electronic health records in the UK and Denmark, matching incident cases of ischaemic stroke to controls by age and sex, and found that those that discontinue OAC have a risk of stroke two to three times greater than those with continuous treatment. (33)

In our population, temporary discontinuation of anti-coagulation was also associated with a greater thromboembolic risk than in people that never initiated OAC therapy, and in those that permanently discontinued. Discontinuation is ostensibly associated with a period of significant clinical risk during which individuals require active, dynamic monitoring. Indeed, rebound hypercoagulability has been postulated to occur transiently in the aftermath of discontinuation, associated with raised blood markers of thrombin production. (34) A cohort study in South Korea reported that discontinuation of DOACs was associated with greater stroke severity at initial presentation, per the National Institute of Health Stroke Scale (NIHSS), than those that discontinued warfarin and those never commenced on anti-coagulation which they postulated was due to this hypercoagulable state. (35)

**Outcomes Following OAC Discontinuation in the Context of a Major Bleeding Event**

This study found that, in the context of a major bleeding event, individuals that discontinued anti-coagulation had an increased risk of SSE and of a further bleeding event compared to those continuously anti-coagulated. Furthermore, our analyses indicated no significant difference in the risk of a subsequent bleed between those that permanently discontinued compared to those that continued anti-coagulation, in those who had experienced a major bleeding event. Whilst the respective cohorts reflect anti-coagulant prescribing status at the time of the
relevant clinical events, there is considerable heterogeneity within the discontinuation cohorts, with regards to the number of, and duration of, discontinuations before and after the event. Thus, the analysis and interpretation of this sequencing is challenging, particularly in the absence of information on the rationales anti-coagulant prescribing decisions within our dataset. Ewen et al. previously found no difference in rates of bleeding events between people with continuous and discontinuous anti-coagulation, although this was in a primary care setting with a shorter follow-up duration of twelve months. (36) Several prior cohort studies, and a meta-analysis, have reported that recommencing anti-coagulation following a bleed is associated with a lower risk of ischaemic stroke and all-cause mortality to those for whom anti-coagulation remained withheld, with no statistically significant difference in the risk of bleeding. (5, 37, 38) However, these have typically focused on single type of bleeding event, for example, gastrointestinal bleeding, or only considered these outcomes in the short-term. Consensus on the optimum time to reinitiate anti-coagulation following a major bleeding event is currently lacking; the American Heart Association recommends re-initiation of anti-coagulation within 7-10 days following an intracranial haemorrhage, whilst others have proposed 10 weeks.(39) Acutely, the risk of further bleeding is likely greater than the risk of stroke or systemic embolism, whilst in the longer-term risk of thromboembolism may exceed that of a recurrent bleed.

Strengths and Limitations
A key strength of our study is the use of national linked data to understand, over a relatively long follow-up period, patterns and inequalities in anti-coagulant prescribing in a real-world AF population, and the effects of discontinuation of anti-coagulation on clinical outcomes. Our results are generalisable to similar AF populations, particularly in those for which there is universal healthcare provision.

However, our study has several possible limitations. Firstly, given the retrospective study design, there may have been unmeasured confounding which could have biased our effect estimates, which could not feasibly be investigated within the context of an RCT.(40) However, in the absence of randomised controlled trials, which would be unethical and infeasible, retrospective observational analyses are the optimal alternative to generate evidence in this context.

Second, since SMR01 and SSCA only include diagnoses relevant to hospital admissions, AF diagnoses in primary care were not captured in our data.(41) Furthermore, a survey of English general practices reported that half of people with AF were managed exclusively in primary care; comparatively, our secondary care AF population is likely at greater risk of the outcomes measured.(42)
Clinical miscoding is a possible risk of utilising data derived from administrative healthcare records. Furthermore, PIS only captures primary care prescribing data, such that secondary care prescriptions of anti-coagulants may thus create a temporal gap within the PIS data. A refill gap of 60 days was thus selected to afford sufficient time for community prescribing to have resumed following a secondary care admission, to reduce the potential for erroneous assignment of people to the discontinuous cohort following hospital discharge, since the reason for discontinuation is not recorded in PIS. Assuming anti-coagulation continued to be prescribed and dispensed, people with poor adherence, and potentially those with sub-therapeutic doses of warfarin, would be classified within the continuous cohort. Our dataset also does not contain information related to prescriber decision-making, or on procedures such as AF ablation or cardioversion, and thus the rationales for OAC non-prescribing, initiation, and discontinuation, are uncertain.

A further limitation of the study is that the study was undertaken during a transition period in anti-coagulant prescribing, in which DOACs replaced warfarin as the preferred anti-coagulant in people with AF. Indeed, DOACs have an improved safety profile, and do not have the monitoring requirements of warfarin, and thus may be associated with greater adherence.

Finally, given the heterogeneous patterns of adherence for anti-coagulation, our definition for discontinuation may not have adequately captured the risks of our outcome measures for all individuals in this cohort. Indeed, individuals within this cohort may have had significantly different time periods in which they were not anti-coagulated.

Future Research

Harmonisation of definitions and methodologies in the evaluation of discontinuation of anti-coagulation would be highly valuable in aiding comparisons since there is significant heterogeneity in the existing literature.

Given the under-utilisation of thromboprophylaxis, and high discontinuation rates observed in our analyses and in the wider literature, further research is critical to elucidate the rationales underlying decision-making more clearly, by clinicians and patients, around anti-coagulant prescribing. Indeed, this will allow the development of targeted interventions aimed at promoting appropriate OAC initiation on diagnosis of AF and mitigating OAC discontinuation, such that stroke prevention may be optimised; patient-centred approaches which promote shared decision-making between clinicians and patients are valuable in supporting adherence.(43) This is particularly important since there is increasing evidence that the lack of monitoring for DOACs, whilst convenient, may be deleterious to persistence; monitoring
appointments afford healthcare professionals the opportunity for continued patient education to reinforce the rationale for anti-coagulation. (44)

Further research is necessary to establish an optimal approach to management of anti-coagulants in adults with AF in the context of major bleeding events, given the lack of consensus amongst clinicians, and consequent variation in real-world clinical practice. This would support the identification of individuals who may safely recommence anti-coagulation at the appropriate timepoint following a bleed, as well as those in whom future anti-coagulation is potentially contra-indicated, optimising clinical outcomes.

Conclusion
Considerable inequalities in OAC prescribing exist for people with AF in Scotland, which is of particular significance since non-initiation and discontinuity of anti-coagulation are associated with poorer clinical outcomes, including increased SSE risk.

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Conflicts of Interest
RM, FM, GC, TQ, and CG have received research grants from Bristol Myers Squibb and Pfizer UK. TQ is a data monitoring committee chair for Novo Nordisk. RT is currently employed by Pfizer UK and owns Pfizer stocks/shares. KP is currently employed by Bristol Myers Squibb. SL was previously employed by Bristol Myers Squibb and owns stocks and shares in Pfizer and Bristol Myers Squibb.

Authors’ Contributions
Ryan Mulholland - Data curation, Formal analysis, Writing-original draft
Francesco Manca - Data curation, Writing-review & editing
Giorgio Ciminata - Data curation, Writing-review & editing
Terry Quinn - Conceptualisation, Methodology, Writing-review&editing
Robert Trotter - Funding acquisition, Writing-review&editing
Steven Lister - Conceptualisation, Methodology, Funding acquisition, Writing-review&editing
Kevin Pollock - Funding acquisition, Supervision, Writing-review&editing
Claudia Geue - Conceptualisation, Funding acquisition, Methodology, Supervision, Writing-review&editing

References


### Tables and Figures

#### Table 1

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<thead>
<tr>
<th>Status</th>
<th>Definition</th>
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<tr>
<td>Never Started</td>
<td>Individuals with an incident AF event during the study that were not prescribed an oral anti-coagulant</td>
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<td>Continuous OAC Therapy</td>
<td>Individuals with an incident AF event during the study that were prescribed an oral anti-coagulant with no refill gaps exceeding the defined threshold for discontinuation</td>
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<td>Discontinuous OAC Therapy</td>
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<td>Cessation of OAC Therapy</td>
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<td>33.88</td>
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<td>Mean (SD)</td>
<td>80.72 (9.52)</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
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<td>15,182</td>
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<tr>
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<td>57.78</td>
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<tr>
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<td>Grouped Charlson Index</td>
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<td>41.25</td>
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<td>1-2 (City) %</td>
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<tr>
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<td>70.86</td>
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<td>3-6 (Towns) %</td>
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<tr>
<td>7-8 (Rural) %</td>
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<tr>
<td>SIMD</td>
<td>1 %</td>
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<tr>
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<td>23.42</td>
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<td>24.08</td>
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<tr>
<td>3 %</td>
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<td>4 %</td>
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<td>3,895</td>
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<td>Prior Stroke %</td>
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<td>%</td>
<td>6.15</td>
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<tr>
<td>Previous anti-platelet</td>
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</tr>
<tr>
<td>%</td>
<td>59.07</td>
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<tr>
<td>Frailty Score</td>
<td>Low risk &lt;5</td>
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<td>52.99</td>
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<td>45.83</td>
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<td>25.43</td>
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</table>
Figure 2
Figure 3

OAC Status
Age >75
Male Sex
SIMD Quintile
Frailty Risk Score Category
Moderate Risk (5-15)
High Risk (>15)

Subhazard Ratio

Discontinuation
Cessation

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Figure 4
Table and Figure Legends

Table 1 Cohort Definitions

Table 2 Descriptive statistics by anti-coagulation status

Figure 1 Outline of identification of AF population and formation of cohorts utilised in analyses, including sub-group analyses.

Figure 2 SSE Risk A) Never Started vs Discontinuous and Cessation B) Continuous vs Discontinuous and Cessation C) Discontinuous* vs Cessation *reference Truncated upper confidence intervals: ★ 16.49 ★ 6.48 ★ 17.75 ★ 6.66 ★ 8.43

Figure 3 SSE risk following major bleeding event A) Continuous vs Cessation and Discontinuous B) Discontinuous* vs Cessation *reference. Analyses were also adjusted for time off anti-coagulation.

Figure 4 Recurrent bleeding risk A) Continuous vs Cessation and Discontinuous B) Discontinuous* vs Cessation *reference. Truncated upper confidence intervals: ★ 11.41 ★ 12.49 Analyses were also adjusted for time off anti-coagulation.
Aim
To evaluate the effect of inequalities in oral anticoagulation (OAC) prescribing on outcomes in people with AF

Methods
Retrospective cohort study using linked Scottish healthcare data

AF Population
- Diagnosed 2009–2015
- Age > 65
- CHA2DS2-VASC 2

Cohorts
- Never Started
- Continuation
- Discontinuation
- Discontinued

5 years follow-up from date of AF diagnosis

Outcome
- Stroke/systemic embolism
- Death
- Major bleeding

Inverse probability of treatment weighting (IPTW)-adjusted Cox regression and competing-risks regression to compare risks of outcomes between cohorts

Results
- Over half of the AF population were never prescribed OAC
- Non-prescribing and discontinuous prescribing of OAC was associated with:
  - Low socio-economic status
  - Elevated frailty score
  - Age 75 or greater
- Stroke risk was significantly greater in those with discontinuous compared to continuous OAC
- No significant difference in bleeding risk between continuous OAC compared to those that permanently discontinued

Take-home Messages
- Considerable inequalities in OAC prescribing
- Discontinuation or cessation of OAC is associated with significant thromboembolic risk not offset by a decreased risk of bleeding

Graphical Abstract
159x95 mm (x DPI)
Ryan Mulholland Biography

Ryan joined the Health Economics and Health Technology Assessment (HEHTA) team at the University of Glasgow in 2022. He obtained his medical degree from the University of Edinburgh in 2018 and completed a MSc in Precision Medicine and Pharmacological Innovation at the University of Glasgow in 2020.

Ryan’s current work is focused on the use of real-world evidence in health technology assessment (HTA), particularly within oncology and cardiovascular disease, and evidence synthesis. His research interests also include analysis of linked health data, the economics of precision medicine, and economic evaluation alongside clinical trials, particularly within the field of oncology.